IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: El-Naggar *et al.* Examiner: Kwon, Brian Yong S.

Serial No.: 09/943,048 Group Art Unit: 1614

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Title: **TREATMENT OF INFLAMMATORY, CANCER, AND THROMBOSIS DISORDERS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF OF APPELLANT

This Reply Brief is in reply to the Examiner's Answer, mailed November 16, 2006.

GROUND OF REJECTION 1

Claims 23-24 was rejected under 35 U.S.C.§ 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner's Answer withdrew the rejection of claims 23-24 under 35 U.S.C.§ 112, first paragraph.

GROUND OF REJECTION 2

Claim 15 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner's Answer withdrew the rejection of claim 15 under 35 U.S.C.§ 112, second paragraph.

GROUND OF REJECTION 3

Claims 10-13, 18-21 and 23-24 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221).

Appellants respectfully contend that claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro, because Hedden in view of Langhoff and Shapiro does not teach or suggest each and every feature of claims 10 and 18.

Appellants argue *infra* that Hedden in view of Langhoff and Shapiro does not teach or suggest the following features:

"low dose aspirin in the amount of 70-85 mg"; and

"an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof".

LOW DOSE ASPIRIN IN THE AMOUNT OF 70-85 MG

A first reason why claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro is that Hedden in view of Langhoff and Shapiro does not teach or suggest the feature: "low dose aspirin in the amount of 70-85 mg".

The Examiner's Answer, page 6 argues that "Hedden teaches the use of COX-2 inhibitor such as celecoxib and rofecoxib for the treatment of inflammatory disorders including arthritis ", which Appellants agree with.

The Examiner's Answer, page 6 argues that "Langhoff teaches the use of low dose aspirin (in dosage range of 30mg-75mg) for the treatment of anti-inflammatory disorder including

rheumatism and arthritis (claims 18-19)", which Appellants disagree with..

Appellants disagree with the preceding argument in the Examiner's Answer with respect to Langhoff, because claims 18-19 of Langhoff teach the use of **a composition** for the treatment of inflammatory disorder including rheumatism and arthritis, said composition comprising a) at least a ω-3-unsaturated fatty acid and/ or its physiologically compatible derivative; (b) vitamin E; (c) vitamin C; and (d) acetylsalicylic acid (i.e., aspirin) in a dosage range of 30mg-75mg. Claims 18-19 of Langhoff do not teach the use of acetylsalicylic acid (in a dosage range of 30mg-75mg) outside of the preceding **composition** for treating inflammatory disorder.

The issue is whether it is obvious to include low-dose aspirin (i.e., aspirin in a dosage range of 30-75 mg as allegedly taught by Langhoff) in Hedden's composition for treating inflammatory disorder.

Given what Langhoff teaches in light of what is known in the prior art as to the effectiveness of various dosages of aspirin for treating inflammatory disorder, Appellants contend that it is not obvious to include low-dose aspirin in Hedden's composition for treating inflammatory disorder. In particular, Appellants' argument is based on the following four considerations which will be explored *infra* in depth.

1. Langhoff does not teach the use of low dose aspirin for treating inflammatory disorder other than in a specific composition comprising: ω-3-unsaturated fatty acid, vitamin E, and vitamin C.

2. Langhoff example, using test data, does not support the use of aspirin in a dosage range of 30-75 mg for treating inflammatory disorder. In addition, the test data reported in Langhoff is

subjective and not statistically based, and therefore does not meet rigorous standards of proof necessary for convincing the scientific community to draw conclusions from the test results. Therefore, Langhoff does not provide test data that supports the conclusion alleged in the Examiner's Answer regarding the alleged effectiveness of low-dose aspirin for treating inflammatory disorder.

3. It is well known in the art, based on credible published studies, that much higher doses of aspirin than 30-75 mg are required for implementing therapeutically effective treatment of inflammatory disorder.

4. From the preceding considerations (items 1, 2, 3), Appellants respectfully contend that Langhoff does not present sufficient evidence to persuade a person of ordinary skill in the art to add low-dose aspirin to Hedden's composition for treating inflammatory disorder, given the well-known finding in the prior art that much higher doses of aspirin than 30-75 mg are required for implementing therapeutically effective treatment of inflammatory disorder.

1. Langhoff does not teach the use of low dose aspirin for treating inflammatory disorder other than in the specific composition comprising: ω-3-unsaturated fatty acid, vitamin E, and vitamin C.

In consideration of the fact that Langhoff appears published in the German language, Appellants present in Tables 1 and 2 below, to the best of Appellants' ability, an English translation of the specific portions of Langhoff cited by the Examiner's Answer.

Table 1. Citations to Langhoff (page 1 (57) abstract; page 2, lines 32-35; page 2, lines 57-68)

Cite in Langhoff	Text of Citation
Page 1 (57) Abstract	The invention is a pharmaceutical compound, containing at least a ω-3-unsaturated fatty acid and/or its physiologically compatible derivatives, vitamin E, vitamin C, and acetylsalicylic acid. This compound is used for the treatment of rheumatic-arthritic diseases and to prevent cardiovascular diseases in humans and animals.
Page 2, lines 32-35	It was one task of the invention to provide a pharmaceutical compound that is an improvement for the treatment and prevention of inflammation processes in the body, particularly for treating and preventing rheumatic-arthritic problems as well as preventing cardio-vascular problems.
Page 2, lines 57-68	For the invention, the acetylsalicylic acid is used in very minute amounts: less than 75 mg/day, preferably less than 60 mg/day, so the effect of hindering *thrombozyten* aggregation was not observed. The known side effects of acetylsalicylic acid, such as stomach bleeding or pseudo-allergic reactions, did not occur. No known substance can attain the same effect of hindering inflammation of rheumatic-arthritic and cardio-vascular diseases with such minimal side effects as does this invention compound. The compound is intended for oral dispensing and can be considered in various different forms: powder, tablet, pill, capsule, solution, concentrate, syrup, suspension, gel, or in the form of a dispersion. The compound can be prescribed so that the total amount of acetylsalicylic acid available to the body is between 30 and 75 mg per day, preferably between 35 and 45 mg per day (for a person with a body weight of approximately 75 kg). The appropriate quantity…

Table 2. Citation to Langhoff (Claims 1 and 14-19)

Cite in Langhoff	Text of Citation
Claims 1, 14-19	1. Pharmaceutical compound encompassing (a) at least a ω-3-unsaturated fatty acid and/ or its physiologically compatible derivative (b) vitamin E, (c) vitamin C, and (d) acetylsalicylic acid. 14. Remedy according to claim 13 for the treatment and prevention of rheumatic-arthritic diseases as well as prevention of cardio-vascular diseases. 15. Remedy according to claim 14 for the treatment and prevention of rheumatism and arthritis and for the prevention of heart attack, arteriosclerosis, *stenos*, and thrombosis. 16. Use of the compound as defined in any of the claims 1 through 12 for the treatment of inflammation diseases in humans or in animals. 17. Use according to claim 16 for the treatment and prevention of rheumatic-arthritic diseases and/or prevention of cardio-vascular diseases. 18. Use according to claim 17 for the treatment and prevention of rheumatism and arthritis and prevention of heart attack, arteriosclerosis, *stenoe*, and thrombosis. 19. Use according to any of the claims 16 through 18 in a dose of 30 to 75 mg of acetylsalicylic acid per day.

From Table 2, claims 18-19 (relied upon in the Examiner's Answer) show that Langhoff claims the use of low-dose aspirin only in a pharmaceutical compound encompassing a ω-3-

unsaturated fatty acid, vitamin E, and vitamin C, for the treatment of rheumatic-arthritic diseases and for the prevention of cardiovascular diseases. Langhoff does not claim the use of low-dose aspirin outside of the preceding pharmaceutical compound.

None of the citations to Langhoff in Tables 1 and 2 teach or suggest that aspirin (i.e., acetylsalicylic acid) having a dosage not exceeding 75 mg contributes to the treatment of rheumatic-arthritic diseases outside of Langhoff's disclosed pharmaceutical compound.

In addition, none of the citations to Langhoff in Tables 1 and 2 teach or suggest that aspirin having a dosage not exceeding 75 mg contributes, by itself, to the treatment of rheumatic-arthritic diseases.

Moreover, none of the citations to Langhoff in Tables 1 and 2 teach or suggest that Langhoff's pharmaceutical compound would be less effective in treating rheumatic-arthritic diseases if the aspirin were removed from the pharmaceutical compound.

2. Langhoff example, using test data, does not support the use of aspirin in a dosage range of 30-75 mg for treating inflammatory disorder.

Appellants present next an English translation of the example on page 5 of Langhoff, which indicates that aspirin having a dosage not exceeding 80 mg does not contribute to the treatment of rheumatic-arthritic diseases.

CITATION TO EXAMPLE IN PAGE 5 OF LANGHOFF

For the following example cod liver oil, vitamin E, vitamin C and acetylsalicylic acid are used in pure forms. An experiment using flax oil for the source of the ω-3-unsaturated fatty acid (α linoleic acid) produced the same results.

The inflammation hindering effect of the following formulation is compared for a person (body weight around 75 kg), who suffers primarily from rheumatic-arthritic diseases as well as from a mild cardio-vascular disease.

A) 10 g cod liver oil, 1000 mg vitamin E, 1000 mg vitamin C

B) 80 mg acetylsalicylic acid

C) 250 mg vitamin E, 40 mg acetylsalicylic acid

D) 50% of A) and 50% of B)

The dispensing of the above named amounts took place daily, in individual doses, over a period of fourteen weeks. Using a value system (1= very good; 2=good; 3=satisfactory; 4= sufficient; 5=barely noticeable alleviation; 6=no alleviation), the test subject described the results thus:

compound	evaluation
A	2
B	6
C	3
D	1

END OF CITATION TO EXAMPLE IN PAGE 5 OF LANGHOFF

Appellants conclude from the preceding example on page 5 of Langhoff as follows:

(1) The evaluation of "6" for compound B) indicates that 80 mg acetylsalicylic acid is not effective in treating rheumatic-arthritic diseases;

(2) An evaluation of "3" for compound C), in comparison with the evaluation of "6" for compound B), indicates that the "satisfactory" alleviation of the rheumatic-arthritic diseases is due to the 250 mg vitamin E and not to the acetylsalicylic acid; and

(3) An evaluation of "1" for compound D), in comparison with the evaluation of "6" for compound B), indicates that the "very good" alleviation of the rheumatic-arthritic diseases is due to the (10 g cod liver oil, 1000 mg vitamin E, 1000 mg vitamin C) and not to the acetylsalicylic acid. Appellants note that the conclusion in the Examiner's Answer, page 11 that the results for compound D) versus compound B) "shows a superior anti-inflammatory effect" is incorrect, because the Examiner's Answer fails to recognize that the primary difference between compounds B) and D) that accounts for the relatively better performance of compound D) is the 5 g cod liver oil, 500 mg vitamin E, 500 mg vitamin C that is present in compound D) and is absent in compound B).

(4) The conclusion in the Examiner's Answer, page 11 that the results for compound D) versus compound A) "shows a superior anti-inflammatory effect" is incorrect, because the Examiner's Answer fails to recognize that the difference in the evaluation of "1" and "2" for compounds D) and A), respectively, for only one data sample is not statistically insignificant.

(5) Appellants assert that even if the data in the example on page 5 of Langhoff were favorable to the position taken in the Examiner's Answer (which it is not), the data in this Langhoff example is subjective, not statistically based, and does not meet rigorous standards of

proof necessary for convincing the scientific community to draw conclusions from the test results. Therefore, Langhoff does not provide sufficient test data at a quality level that would support the conclusion in the Examiner's Answer regarding the alleged effectiveness of low-dose aspirin for treating inflammatory disorder.

3. It is well known in the art, based on credible published studies, that much higher doses of aspirin than 30-75 mg are required for implementing therapeutically effective treatment of inflammatory disorder.

Appellants respectfully contend that it is known in the art that low dose aspirin in doses of 30-75 mg is not effective in the treatment of inflammatory disorder, as evidenced by numerous published papers. Appellants next cite the abstract of several articles to illustrate that much higher doses of aspirin that 30-75 mg are required for therapeutically effective treatment of inflammatory disorder.

See Calin A. "Pain and inflammation", Am J Med. 1984 Sep 10;77(3A):9-16. The abstract of the preceding reference (Calin) is as follows:

> "The traditional "aspirin first" approach to the treatment of osteoarthritis and rheumatoid arthritis is undergoing serious reappraisal. Aspirin and acetaminophen are equipotent in their analgesic efficacy; however, aspirin is associated with a higher incidence of side effects. Acetaminophen should therefore be used as first-line therapy for the treatment of osteoarthritis since reduction of pain is the primary therapeutic objective. Analgesic doses of aspirin (up to 3,900 mg per day) do not produce an anti-inflammatory effect and thus are not beneficial in the treatment of rheumatoid arthritis. **Only high doses of aspirin (4 to 6 g per day) used for a sustained period produce an anti-inflammatory effect.** Since many patients with

rheumatoid arthritis cannot tolerate long-term use of anti-inflammatory doses of aspirin, it may be preferable to initiate therapy with one of the newer nonsteroidal anti-inflammatory drugs."

See, Gomes I, "Aspirin: a neuroprotective agent at high doses?", Natl Med J India. 1998 Jan-Feb;11(1):14-7. The abstract of the preceding reference (Gomes) is as follows:

"Aspirin, acetylsalicylic acid, is routinely used in clinics as an analgesic, antipyretic and in the secondary prevention of stroke. These effects are caused by low doses of the drug (0.3-3.6 g/day) through the inhibition of cyclo-oxygenase, the enzyme responsible for prostaglandin synthesis. **Higher doses of aspirin (4-6 g/day) are used in the treatment of inflammatory conditions such as rheumatoid arthritis** and recent laboratory findings suggest that it could play a role in neuroprotection against glutamate excitotoxicity. This article reviews the possible mechanisms of action of high-dose aspirin in neuroprotection."

See Appelrouth DJ, Baim S, Chang RW, Cohen MH, Englund DW, Germain BF, Hartman SS, Jaffer A, Mullen BJ, Smith FE, "Comparison of the safety and efficacy of nabumetone and aspirin in the treatment of osteoarthritis in adults", Am J Med. 1987 Oct 30;83(4B):78-81. The abstract of the preceding reference (Appelrouth et al.) is as follows:

A six-month, multicenter, double-blind study compared the efficacy and safety of two therapeutic regimens in 332 patients with osteoarthritis. The patients received either 1,000 mg of nabumetone as a single bedtime dose or **900 mg of aspirin in four divided doses**. At the end of the study, patients in both treatment groups showed significant improvement from baseline for all five parameters; no statistically or clinically significant differences were observed between the groups. The safety data did reveal clinically and statistically significant differences

between the groups. Aspirin-treated patients experienced a greater frequency of withdrawal from the study because of adverse experiences (34 percent versus 13 percent), a greater incidence of having at least one treatment-related adverse experience (73 percent versus 52 percent), a greater percentage of patients with at least one moderate or severe treatment-related adverse experience (47 percent versus 22 percent), and a greater percentage of patients with treatment-related adverse experiences affecting the gastrointestinal system (43 percent versus 32 percent) or the inner ear (32 percent versus 10 percent). The results of this study demonstrated that nabumetone, 1,000 mg at bedtime, is as efficacious as **aspirin, 900 mg four times daily**, produces fewer adverse effects, and is indicated in the treatment of osteoarthritis.

See Fries JF, Ramey DR, Singh G, Morfeld D, Bloch DA, Raynauld JP, "A reevaluation of aspirin therapy in rheumatoid arthritis", Arch Intern Med. 1993 Nov 8;153(21):2465-2471. The abstract of the preceding reference (Fries et al.) is as follows:

"Aspirin therapy has been largely superseded by prescription nonsteroidal anti-inflammatory drug (NSAID) therapy in rheumatoid arthritis, in part because of premarketing studies suggesting lesser toxic effects for NSAIDs than for aspirin. This study evaluates these toxic effects in a postmarketing population of patients with rheumatoid arthritis. METHODS: We studied 1521 consecutive courses of aspirin and 4860 courses of NSAIDs in patients with rheumatoid arthritis from eight Arthritis, Rheumatism, and Aging Medical Information System Post-marketing Surveillance Centers. Toxicity index scores were generated from symptoms, laboratory abnormalities, and hospitalizations, weighted for variable severity and severity of side effect. RESULTS: The toxicity index was only 1.37 (SE = 0.10) for aspirin and 1.87 to 2.90 for selected nonsalicylate NSAIDs. These differences were consistent across centers and remained after statistical adjustment for differing patient characteristics. There was a different toxicity with different

aspirin preparations, with a score for plain aspirin of 1.36 (SE = 0.23), for buffered aspirin of 1.10 (0.20), and for enteric-coated aspirin preparations of 0.92 (0.14). Most important, there were strong dose effects, with a score of 0.73 (0.09) for **651 to 2600 mg daily**, 1.08 (0.17) for 2601 to 3900 mg, and 1.91 (0.38) for **more than 3900 mg**. The average aspirin dose taken was only 2665 mg/d, approximately eight "tablets," compared **with 3600 to 4800 mg/d** used in the 16 pivotal premarketing studies reviewed. Average NSAID doses were, on the other hand, lower in premarketing trials (eg, naproxen 500 mg/d vs 773 mg/d in the Arthritis, Rheumatism, and Aging Medical System clinical practices). CONCLUSIONS: Aspirin therapy, in doses commonly employed in practice, has an excellent safety profile in rheumatoid arthritis, and it is the least costly NSAID. The safety advantage is explained primarily by a dose effect and secondarily by possible differences between formulations. Newer management strategies for rheumatoid arthritis emphasize NSAID use as symptomatic therapy and use of disease-modifying anti-rheumatic drug therapy for anti-inflammatory objectives. Thus, the original recommendation for "anti-inflammatory" doses of aspirin now is less easily justified. Aspirin therapy merits reconsideration as adjunctive therapy for the management of rheumatoid arthritis."

See Edwards, W., "Etodolac, aspirin, and placebo in patients with rheumatoid arthritis: a 12-week study", Clin Ther. 1983;5(5):495-503. The abstract of the preceding reference (Edwards) is as follows:

"Etodolac, aspirin, and placebo were evaluated for efficacy and safety in 18 patients with adult-onset, active rheumatoid arthritis. This was a 12-week, double-blind, parallel-group study divided into drug titration and maintenance periods and preceded by a washout period of up to two weeks. The mean daily maintenance doses of etodolac and aspirin were **394 mg and 4,414 mg**, respectively. Etodolac was significantly (P less than or equal to 0.05) more effective than placebo in five

of ten clinical variables of efficacy: number of painful joints, number of swollen joints, pain intensity, erythrocyte sedimentation rate, and patients' overall assessments. Aspirin was significantly more effective than placebo in only two assessments: number of painful joints and pain intensity. One patient on etodolac, two patients on aspirin, and four patients on placebo had to be withdrawn from the trial because of insufficient therapeutic response. One patient in the placebo group was withdrawn from the study because of a pruritic rash. Mild to moderate gastrointestinal complaints occurred in all three treatment groups: in three patients taking etodolac, three taking aspirin, and two taking placebo."

See Kolarz G., "Double-blind, cross-over, international multicentre investigation of two doses of indoprofen compared with ASA and placebo in rheumatoid arthritis", Eur J Rheumatol Inflamm., 1981;4(1):53-59. The abstract of the preceding reference (Kolarz) is as follows:

"Indoprofen **600 mg or 1000 mg/day, ASA 3600 mg/day** and placebo were administered in randomized sequences according to a multiple 4 x 4 latin square design, balancing the treatments, periods and residual effects. Each treatment lasted 7 days. A total of 98 patients suffering from classical or definite rheumatoid arthritis completed the study. Analysis of the effectiveness indicates that both doses of indoprofen and ASA are significantly more active than placebo; indoprofen 1000 mg/day was the treatment preferred in most of the cases. Both doses of indoprofen were better tolerated than ASA."

In summary, the preceding evidence demonstrates that aspirin doses of 394 mg to 6,000 mg are therapeutically effective in the treatment of inflammatory disorder.

Appellants note that, outside of Langhoff whose data does not support the conclusion reached in the Examiner's Answer, the Examiner's Answer has not provided any credible

evidence to support the contention in the Examiner's Answer that low-dose aspirin of 30-75 mg is therapeutically effective for treating inflammatory disorder.

4. From the preceding considerations (items 1, 2, 3), Appellants respectfully contend that Langhoff does not present sufficient evidence to persuade a person of ordinary skill in the art to add low-dose aspirin to Hedden's composition for treating inflammatory disorder, given the well-known finding in the prior art that much higher doses of aspirin than 30-75 mg are required for implementing therapeutically effective treatment of inflammatory disorder.

Langhoff does not teach or suggest that aspirin having a dosage not exceeding 75 mg contributes to the treatment of rheumatic-arthritic diseases outside of Langhoff's disclosed pharmaceutical compound comprising ω-3-unsaturated fatty acid, vitamin E, and vitamin C. However, Hedden's compound comprises primarily a COX-2 inhibitor such as celecoxib and rofecoxib for the treatment of inflammatory disorders and does not comprise ω-3-unsaturated fatty acid, vitamin E, and vitamin C. Therefore, it is not obvious to modify Hedden to add aspirin in the amount of 70-85 mg to a standard therapeutic dose of COX2 inhibitor for the treatment of inflammatory disorder.

Langhoff's example, using test data, does not support the use of aspirin in a dosage range of 30-75 mg for treating inflammatory disorder. In addition, the test data reported in Langhoff is subjective and not statistically based, and therefore does not meet rigorous standards of proof necessary for convincing the scientific community to draw conclusions from the test results that the Examiner's Answer alleges. Moreover, the Examiner's Answer has not provided any credible scientific evidence (Langhoff or otherwise) allegedly demonstrating that low dose aspirin in doses

of 30-75 mg is therapeutically effective in the treatment of inflammatory disorders. Therefore, it is not obvious to modify Hedden to add aspirin in the amount of 70-85 mg to a standard therapeutic dose of COX2 inhibitor for the treatment of inflammatory disorder.

As explained *supra*, it is well known in the art (based on credible published studies) that much higher doses of aspirin than 30-75 mg are required for implementing therapeutically effective treatment of inflammatory disorder. As also explained *supra*, Langhoff does not present sufficient evidence to persuade a person of ordinary skill in the art to include low-dose aspirin in Hedden's composition for treating inflammatory disorder, given the well-known finding in the prior art that much higher doses of aspirin than 30-75 mg are required for implementing therapeutically effective treatment of inflammatory disorder.

AN ANTIOXIDANT SELECTED FROM THE GROUP CONSISTING OF A FLAVANOID, A FLAVONOID, AN ISOFLAVONE, AND COMBINATIONS THEREOF

A second reason why claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro is that Hedden in view of Langhoff and Shapiro does not teach or suggest the feature: "an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof".

The Examiner's Answer, page 6 argues: "Shapiro (US 6444221) teaches the use of flavonoids, flavanoids and isoflavones (i.e., daidzin, genistein, quercetin, silymarin, etc...) as antioxidants having functional equivalent property for the treatment of inflammatory disease conditions (column 9, line 52 thru column 10, line 32; column 20, line 47 thru column 21, line 8)."

In response, Appellants contend that Shapiro teaches that the disclosed flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease only in combination with carbonyl trapping agents. See Shapiro, col, 10, lines 43-51. See also, Shapiro, col, 10, lines 59-67 ("In another preferred embodiment, use of a primary agent in combination with a clinically effective anti-oxidant and lipid peroxidation inhibitor co-agent may be of particular benefit in preventing or ameliorating forms of chronic inflammation by incorporating two pharmacological strategies, the sequestering of cytotoxic aldehydes and ketones generated at sites of chronic inflammation and the sequestering of activated oxygen chemical species generated earlier in the non-enzymatic inflammatory cascade."). In Shapiro's composition, the carbonyl trapping agent is the primary ingredient and the antioxidant is one of several alternative secondary ingredients. Shapiro does not teach that the antioxidant by itself is therapeutically effective in treating inflammatory disease.

Therefore, Appellants respectfully contend that Shapiro does not teach that the disclosed flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease in combination with low dose aspirin and COX2 inhibitor, since aspirin and COX2 inhibitor are not carbonyl trapping agents. Accordingly, it would not be obvious to add the disclosed flavonoids, flavanoids and isoflavones as antioxidants to a composition of aspirin and COX2 inhibitor for the purpose of treating of inflammatory disease.

Conclusion

Based on the preceding arguments, Appellants respectfully maintain that claims 10 and 18 are not unpatentable over Hedden in view of Langhoff and Shapiro, and that claims 10 and 18 are

in condition for allowance. Since claims 11-13 and 24 depend from claim 10, Appellants contend that claims 11-13 and 24 are likewise in condition for allowance. Since claims 19-21 and 23 depend from claim 18, Appellants contend that claims 19-21 and 23 are likewise in condition for allowance.

GROUND OF REJECTION 4

Claims 15 and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6,541,613B2).

The Examiner's Answer rejected claims 15 and 22 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hedden *et al.* (WO 01/45705) in view of Langhoff (DE 19855426 A1) and Shapiro (US 6,444,221), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248) and Hendeler (US 6,541,613B2).

Since claims 15 and 22 respectively depend from claims 10 and 18, which Appellants have argued *supra* to not be unpatentable over Hedden in view of Langhoff and Shapiro under 35 U.S.C. §103(a), Appellants maintain that claims 15 and 22 are likewise not unpatentable over Hedden in view of Langhoff and Shapiro Jones in view of Smith and further in view of Burch, Drug Facts and Comparison, and Hendeler under 35 U.S.C. §103(a).

SUMMARY

In summary, Appellant respectfully requests reversal of the March 1, 2006 Office Action rejection of claims 10-13, 15 and 18-24.

Respectfully submitted,

Jack P. Friedman

Jack P. Friedman
Attorney For Appellant
Registration No. 44,688

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Schmeiser, Olsen & Watts
22 Century Hill Drive, Suite 302
Latham, New York 12110
(518) 220-1850